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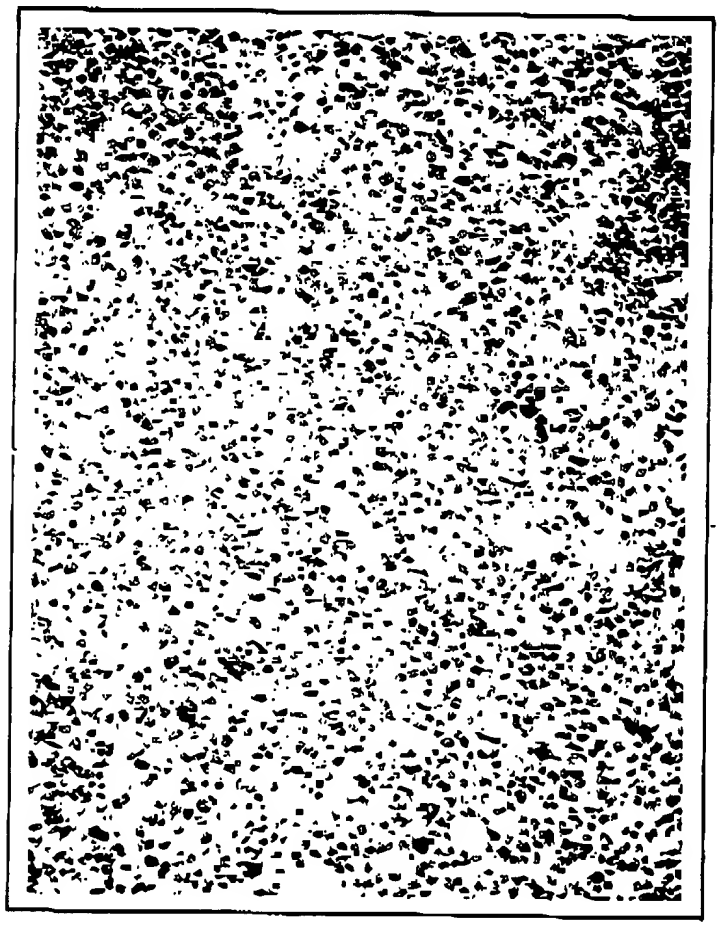

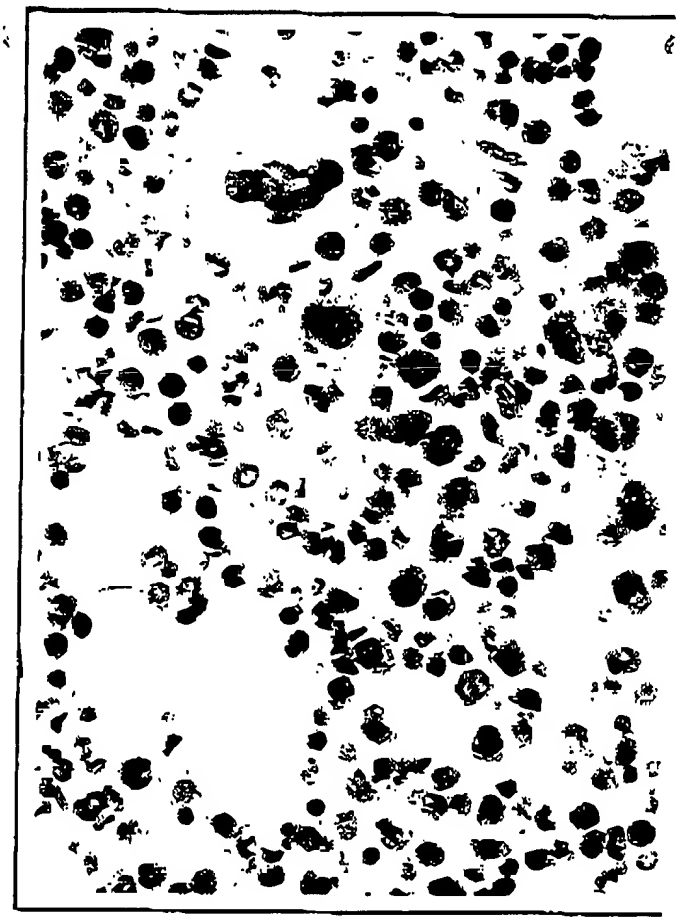

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On the Cover

In the past, surgery resulting in an ostomy meant that the patient had to forsake many of the activities he or she enjoyed before the surgery.

Today, however, ostomy patients no longer must restrict their normal lifestyles. Familial affection, between parent and child or husband and wife, or occupational or societal relationships, need not be limited by the ostomy. The field of enterostomal therapy has provided these patients with the necessary preoperative and postoperative care, as well as rehabilitation, to help patients adjust to their ostomies.

The unified circles on the enterostomal therapist's badge symbolize the teamwork required to reintegrate the ostomy patient into his or her family structure and daily living patterns.

Illustrations © Volk.

In the Next Issue

Jan van Eys, PhD, MD, serves as guest editor of an issue c methotrexate. Topics included in the issue will be folic acid a tagonists in leukemia, methotrexate in gestational trophoblast disease, teratogenicity of folic acid antagonists, molecular basis methotrexate resistance, and clinical use of methotrexate in no malignant diseases, solid tumors, and leukemia and lymphoma.

Bladder cancer will be featured in the Clinical Case Report Serie and the potential for cancer prevention will be discussed in Canc Prevention: Update for Physicians.

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Recent Developments in the Immunodiagnosis of Cancer

Giora M. Mavligit, MD

During the past decade, a new concept of immunodiagnosis of cancer has evolved from a mere intellectual exercise driven by laboratory research in cancer-associated antigens, all the way toward its effective and sometimes critical use in the clinical treatment of some groups of cancer patients. The basic notion underlying the entire field of immunodiagnosis of cancer was to identify a tumor product—either a remnant of normal cell origin synthesized and released by the growing tumor in excessive unregulated amounts, or, we hope, an entirely new "non-self," previously unrecognized entity which may or may not evoke an autogenous immune response by the tumor-bearing host. When rising levels of such tumor product can be detected in body fluids, such as plasma, urine, or cerebrospinal fluid, in serous effusions (pleural, pericardial, or peritoneal), or as a cell-bound component in the bone marrow or in a lymph node (membrane, cytoplasmic, or nucleolar) by the use of specific antibodies, we can cautiously assume that a growing tumor has been immunodiagnosed. It must be emphasized at the outset that immunodiagnosis of cancer is not intended to replace, but rather to supplement conventional diagnostic procedures and to provide the clinician with more powerful tools for better treatment of cancer patients.

To be used effectively in this capacity, such immunodiagnostic procedures must meet several requirements which have to do with the sensitivity and specificity of the tests involved. Although numerous tumor markers have been reported in the medical literature during the past decade, only a handful at their present state of research development can meet even one of these crucial requirements. The transition from a state of being just a tumor marker to a clinically useful diagnostic tool can be summarized as follows:

First, one must be able to interpret the immunodiagnostic test results on an *individual* basis. This means that unlike

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most laboratory research data, which are analyzed by comparing an entire experimental group with a group of controls, using mean or median values to express differences, at the clinical level the immunodiagnostic test for cancer detection must be evaluated like BUN for kidney function or like hemoglobin for anemia, where one does not rely on a p-value to appraise the significance of test results. Second, the immunodiagnostic test results should quantitatively *reflect subtle changes* in the clinical course of the malignant disease, ie, the tumor marker level should go down when the malignant disease responds to therapy and, conversely, it should show persistent rise on tumor growth exacerbation. Third, to justify their relatively high cost and to offer a substantial advantage over more conventional diagnostic procedures, immunodiagnostic tests must *detect subclinical neoplastic disease*, particularly in categories where complete remissions can be routinely achieved by any therapeutic modality (surgery, radiotherapy, or chemotherapy). This is an important aspect in diseases such as lymphoma, leukemia, colorectal carcinoma, testicular and prostatic carcinomas, and some sarcomas, where the immunodiagnostic tests can affirm the completeness (or incompleteness) of the remission achieved. Moreover, early detection of recurrent disease, nondetectable by conventional means, may also be instrumental for prompt therapeutic decisions with a high likelihood of success. Fourth, on the basis of abnormal immunodiagnostic test results suggestive of the presence of recurrent tumor, coupled with other clinical considerations having to do with the biologic behavior of the tumor and the natural history of the disease, the clinician must be able *to make critical decisions*, such as brain irradiation or exploratory laparotomy (depending on the circumstances) even in the absence of pathologic tissue or cytologic diagnosis. Again, the immunodiagnostic tests must have an advantage over the conventional tumor diagnostic procedures in that they would detect subtle rises in tumor marker levels at a time when no tumor is clinically demonstrable and, thus, guide the clinician to take aggressive approaches he would otherwise not likely take at this stage of a given neoplastic disease. Against this conceptual background, one can appraise the recent developments and major advances in the immunodiagnosis of cancer, according to the various tumor markers which have gone through the process of transition from the research laboratory to clinical use in the treatment of cancer patients.

Carcinoembryonic Antigen

During the 16 years following its discovery, carcinoembryonic antigen (CEA) has been studied extensively and has become, despite the controversial issues which seemed to impede its wide use, a routine immunodiagnostic tool in the treatment of some cancer patients. Of particular concern was its lack of specificity, in that it was not exclusively confined, as originally thought, to colon cancer. It was found to be elevated in the plasma of some patients with pancreatic, lung, ovarian, and other miscellaneous carcinomas. Furthermore, it turned out to represent a remnant of normal tissue component incorporated in the network of tumor products which definitely ruled it out as a specific tumor antigen. Despite these apparent shortcomings, extensive clinical studies clearly showed that CEA can be quite useful, particularly as an adjunctive diagnostic tool in patients known to have, or to have had, colorectal cancer. Since elevated plasma levels of CEA were found in approximately 70% of patients with disseminated metastatic colorectal cancer, large-scale screening of the general population for primary colorectal cancer was found to be unproductive at this stage, and this approach was abandoned. The high percentage (30%) of false-negatives has generated a great deal of valid criticism of the usefulness of the assay, which caused further delay in its development.

If the attempt to diagnose primary colorectal cancer by screening the general population with CEA was futile, the case was quite different in the early detection of recurrent disease following surgical resection of the primary tumor.[1-4] For the group of patients who were surgically treated for their primary tumors, serial determination of plasma CEA was definitely fruitful and helped develop the concept of CEA-directed second-look operation. Since no test is perfect and can cover all cases, clinical investigators have learned from experience that patients with a high likelihood of local-pelvic recurrence (mainly after resection of primary rectal or rectosigmoid carcinoma) are less likely to show an elevated CEA prior to or even at the time of such local recurrence. Bearing this limiting factor in mind, one can more judiciously interpret the CEA results in conjunction with sound clinical considerations. In other words, if the clinician suspects a local-pelvic recurrence, a nonelevated CEA cannot safely rule out such tumor recurrence; however, if serial studies show a persistent and progressive pattern of rising CEA, the implication of a recurring tumor is justified and should urge an intensive search in an effort toward tumor localization prior to surgical attempt at possible extirpation. This should not be construed as if in all such cases resection for "cure" is possible. Even if it seems so, one should always assume that other, nonvisible micrometastases also exist in other organs. A good case can therefore be made to supplement surgery with chemotherapy. The latter should precede surgery in cases where the rising CEA has led to the localization of tumor by one of the newly developed imaging techniques, such as computed tomographic (CT) scan, ultrasound, or selective angiography. Such presurgical chemotherapeutic approach would provide valuable information which can be translated from the clinical response of the visible tumor (a falling CEA level or reduction in tumor size) to the nonvisible putative micrometastases.[6] If exploratory (blind) laparotomy were the elected procedure after all attempts at localizing the tumor failed, chemotherapy is again indicated following resection of any tumor found and particularly if surgery were intended for a "cure."

The efforts to localize occult metastases received a new dimension with recent studies using radioisotope-tagged antisera directed against CEA.[7,8] This radioimmune localization of tumor is based on an assumed selective affinity between anti-CEA antibody and the marker-carrying tumor cells. Although some degree of specificity was claimed, certain doubts have been cast in regard to the clinical usefulness of this approach. The difficulties involved in such testing are not trivial: First, one has to administer the antiserum parenterally which, by itself, may evoke an unacceptable, violent immune reaction. Second, the antiserum must be administered in a reasonable excess to overcome the well-documented CEA-anti-CEA complex formation, which should be anticipated if

high levels of circulating CEA can be demonstrated in a given case. With excess antiserum, one can hope that some of it will ultimately reach the occult tumor in a sufficient amount so as to be detected by the radioisotope scanning camera. Third, a great deal of nonspecific attachment of nonimmune IgG can be expected on the surface of tumor cells as they have been shown to express Fc receptors. It is therefore mandatory, perhaps, to use $F(ab')_2$ fractions of the anti-CEA antiserum to ensure that any attachment is indeed indicative of CEA-anti-CEA binding on the surface of the tumor cell.

The question has been frequently raised: "Are we performing too many unnecessary exploratory laparotomies owing to the more extensive use of serial CEA determinations?" Judicious medical evaluation, prior to making the critical decision to explore, must include CT scan of the abdomen with focus on the adrenal glands (a common site for occult abdominal metastases) and, ultimately, selective hepatic angiography. This may reveal hepatic metastases which have evaded detection by scanning techniques. Such systematic approach will minimize the need for blind laparotomies. Still, in the presence of progressively rising CEA, a rare case can be encountered when even an exploratory laparotomy will fail to reveal any tumor. This cannot rule out tumor recurrence, as experience has taught us, since tumor was to be found at a later, more advanced stage. The question is whether to treat such patients with chemotherapy when the only justification is the finding of persistent and progressive rise in CEA. Our own answer to this question is in the affirmative, although others may differ with such an ultra-aggressive approach and may elect to wait-and-see. The contention behind the latter conservative strategy may be: "What if the rising CEA is false-positive?" A few cases have been reported in the literature, but none can be characterized by a persistent and progressive pattern of CEA elevation. Slight fluctuations in CEA were noted after adjuvant chemotherapy with 5-fluorouracil, with a possible reason being fatty metamorphosis of the liver interfering with the normal handling of CEA by the liver, unrelated to excessive CEA production by tumor.[9]

The critical need to establish the persistent and progressive pattern of rising CEA cannot be overemphasized. The frequency of serial determination may be intensified and preferably performed every two weeks, when the index of suspicion rises to a level beyond the routine. Another important factor to keep in mind is the time interval from the original surgery. Recurrent colorectal cancer is common up to three years after surgery. Beyond this interval, it becomes rather sporadic, if not rare, and a rising CEA under such circumstances should always raise the possibility of another primary tumor, such as another colorectal primary or a pancreatic, breast, lung, or ovarian carcinoma. Some of these tumors can present as an unexplained serous effusion (peritoneal, pleural, or pericardial) even without the unequivocal presence of tumor cells. Simultaneous determination of CEA in the plasma as well as in the effusion may clarify the malignant nature of the effusion, particularly if the CEA level in the effusion exceeds that in the plasma. Similar considerations apply to the cerebrospinal fluid in cases suspected for carcinomatous meningitis. While plasma CEA may not be measurably elevated, despite the presence of tumor owing to putative CEA-anti-CEA complexes (assuming that CEA may be autoimmunogenic and therefore evoke antibody response under certain circumstances), the chance for such a theoretical phenomenon in a serous effusion is unlikely and will therefore be less prone to show false-negative CEA results. The subject of naturally occurring CEA-anti-CEA immune complexes which may result in some of the false-negative cases mentioned before is currently under investigation (Mavligit GM, Stuckey SE. manuscript submitted).

Beta$_2$-Microglobulin

Beta$_2$-microglobulin is a nucleated cell-membrane component closely associated with HL-A antigens. Close relationship was also demonstrated between beta$_2$-microglobulin and tumor-associated antigens. Elevated plasma levels (>3 mg/liter) were frequently found in patients with myeloproliferative as well as lympho-proliferative disorders. These elevations were assumed to reflect a rapid cellular turnover, resulting in excessive shedding and release of these small molecules (molecular weight, 11,700 daltons) into the circulation.

Despite the ease of its immunochemical purification and antibody production for an effective radioimmunoassay, the interpretation of plasma levels of beta$_2$-microglobulin in cases of hematologic malignancies for therapy monitoring and prognostic purposes is frequently complicated by subtle changes in glomerular filtration rate, which, by itself, may bring about these changes in beta$_2$-microglobulin, unrelated to the proliferative status of a given hematologic malignancy. Nevertheless, when serial determination of beta$_2$-microglobulin was carried out in the cerebrospinal fluid of patients with acute leukemia and lymphoma, a good correlation was found between elevated levels and CNS involvement by the malignant process.[10] Unlike plasma levels, CSF levels of beta$_2$-microglobulin do not seem to depend on the glomerular filtration rate. Furthermore, simultaneous determination of beta$_2$-microglobulin in the cerebrospinal fluid and the plasma in each case provided a powerful tool to diagnose CNS involvement even earlier than the appearance of positive cytology. Such early diagnosis can be established when the cerebrospinal fluid level exceeds the plasma level of beta$_2$-microglobulin. Following the initiation of intrathecal chemotherapy and/or brain irradiation, serial determination of beta$_2$-microglobulin provided a sensitive monitoring system, in that a falling beta$_2$-microglobulin level always indicated successful therapy, even before the malignant cells disappeared from the CSF. The beta$_2$-microglobulin test is now routinely performed by the clinical laboratory at UT M. D. Anderson Hospital and elsewhere as an adjunctive diagnostic tool in the total treatment plan of patients with acute leukemia and lymphoma.

Pancreatic Carcinoma-Associated Antigens

Despite the lack of substantial progress in the therapeutic approach to carcinoma of the pancreas, a growing interest in its immunodiagnosis has recently generated some new data which may prove to be important in the near future. The comprehensive studies originally designed to clarify whether

CEA was an exclusive marker for colorectal carcinoma yielded unexpected information for patients with carcinoma of the pancreas. First, a higher incidence of positive CEA tests was noted among patients with carcinoma of the pancreas as compared to those with carcinoma of the colon. Second, the levels of CEA measured were frequently higher than what was regularly observed in patients with disseminated colorectal cancer. This fact seems to have not received adequate attention, but in our experience, patients with disseminated carcinoma from unknown primary site, who show a plasma CEA level in the range of thousands of nanograms per milliliter are considered and treated as those with carcinoma of the pancreas. Postmortem examination results frequently proved this clinical assumption to be true. In many cases, biliary obstruction contributed enormously to this phenomenon.[11] Other differences in CEA production also exist between colorectal and pancreatic carcinoma. While in colorectal carcinoma, well-differentiated tumors produced more CEA, an inverse relationship was found between CEA production and tumor differentiation in pancreatic carcinoma.

With a steady increase in the incidence, and since pancreatic carcinoma is rarely cured by surgery, an effort toward screening and early diagnosis in the general population seems plausible. Several groups of investigators are currently involved in the development of new immunoassays, all based on pancreatic carcinoma-associated markers. The marker with an exceptional promise is galactosyl-transferase isozyme II, which was found to be most sensitive (67% correlation with symptomatic carcinoma of the pancreas).[12] Studies on asymptomatic patients will be necessary to optimize the use of this assay in this disease category. A more sophisticated approach, perhaps, was taken by investigators who are trying to purify, immunochemically, pancreatic carcinoma-specific glycoproteins. One of those is the pancreatic oncofetal antigen (molecular weight, 800,000). Initial studies showed again that besides carcinoma of the pancreas, this marker can be detected in other tumor categories, albeit at low levels and with lower incidence.[13] Its use for screening has therefore been ruled out. A second glycoprotein (molecular weight, 1 million) was isolated and purified from the ascitic fluid of a patient with pancreatic carcinoma, and it is designated PCAA.[14] Following several steps of affinity column chromatography, a purified antigen was used to generate antiserum, which was capable of detecting 67% of patients with carcinoma of the pancreas. Again, the PCAA does not seem to be an exclusive marker for carcinoma of the pancreas, but it may be used effectively to monitor and evaluate the completeness of surgical resection (or its incompleteness) and subsequently to detect early tumor recurrence.

Prostatic Carcinoma-Associated Markers

A traditional marker of prostatic carcinoma, the prostatic acid phosphatase (PAP), became a target for the development of a radioimmunoassay purported to replace the enzyme assay with expected augmentation in sensitivity. In the first report by Foti et al.[15] in 1977, 33% of patients with stage A and 79% with stage B prostatic carcinoma showed elevated values of PAP (>8 ng/0.1 ml), compared to only 6% of those with benign hypertrophy of the prostate. Subsequent studies, however, have yielded a much lower incidence of positive tests in either stage A or B (0% to 22% and 26% to 32%, respectively).[16] It is therefore unlikely, in the present state of development, that the radioimmunoassay for PAP can be used for screening; rather, it is possible that it can be used effectively for more accurate staging of known disease. Furthermore, it has also been emphasized that for the diagnosis of an early stage of prostatic carcinoma, the radioimmunoassay is no match for the time-honored, careful, digital examination through the rectum.

Distinctly different from the PAP, a new prostatic carcinoma-specific antigen test is being developed. Studies performed on prostatic carcinoma tissue sections showed approximately 100% incidence of staining with the fluorescent antibodies directed against this antigen, while virtually no staining was noted with any other tissues tested so far. This procedure may be diagnostically useful in the evaluation of biopsy material in patients with adenocarcinoma of unknown primary site. A clue to the prostatic origin of such carcinomas would certainly obviate the need for other unnecessary procedures and perhaps render the therapeutic decisions more judicious.

Miscellaneous Tumor-Associated Antigens

As mentioned earlier, there are numerous tumor markers, and yet only a handful, at this time, carry a potential for immunodiagnosis of cancer. Under the category of "miscellaneous" are included some markers that merit mention in respect to new developments, although the data to support these are preliminary. Perhaps human chorionic gonadotropin (HCG) is the most important in this group. It has been used effectively in the past to monitor patients with gestational tumors (choriocarcinoma and some testicular carcinomas). More recently, radioiodinated HCG has been used to localize conventionally undetectable metastases from testicular cancer by the radioimmunodetection method described earlier in connection with the localization of CEA-producing tumors. Similar considerations of possible difficulties also apply here. The initial report,[17] however, looks rather promising, and more work in this direction is warranted.

The more esoteric tumor markers currently under study are the sialoglycoproteins, which apparently can be detected in 96% of patients' sera and in only 2% of sera from normal donors.[18] Another marker designated as TPA (tissue polypeptide antigen) was discovered in Sweden (molecular weight, 25,000) and can be detected in sera from 75% of patients with several types of cancers, but also in 10% of healthy individuals. The Tennessee antigen (molecular weight, 100,000) is a glycoprotein that has received recent attention, because it can be detected in approximately 80% of patients with lung, colon, gastric, and pancreatic carcinomas. Again, the false-positive rate is approximately 8%. Beta-glucoronidase is a normally occurring enzyme found to be elevated in the CSF of patients with meningeal carcinomatosis. It could provide an early warning for patients with CNS metastases. Finally, the newly discovered nucleolar antigens, thought to be unique for tumor cells, are also found, but with lesser expression, in normal cells.[19]

Monoclonal Antibodies

The broad subject of monoclonal antibodies has been discussed elsewhere (**The Cancer Bulletin**, September-October 1981). The monoclonal antibodies are definitely a new development with a potential in the immunodiagnosis of cancer. For instance, it is quite possible that improved cell sorting, and more accurate diagnosis of neoplastic cells, can be achieved by using monoclonal antibodies in lymphoma and leukemia involving the bone marrow or lymph nodes. Monoclonal antibodies were used to detect a non-CEA antigen in the blood of patients with colorectal cancer[20] and another antigen unique for malignant melanoma.[21] Nevertheless, a word of caution may be appropriate here. It is possible that the unique feature of the monoclonal antibody, ie, to detect only a limited portion from the entire phenotype characterizing the antigenic moiety in a given tumor, may be counterproductive as far as immunodiagnosis of cancer is concerned. This is particularly true if one intends to detect shedding antigens in the circulation. If the shed antigenic material which predominates in circulation is not detected by a highly specific monoclonal antibody, a false-negative test may be interpreted erroneously. Therefore, carefully designed clinical trials will be necessary to show whether the monoclonal antibodies will have any advantage over the conventionally prepared antisera in the immunodiagnosis of cancer.

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